IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re PATENT APPLICATION of
Tsokos, et al.

Group Art Unit: 1635

Serial No.: 10/772,704

Examiner: Chong, K.

Filed: February 5, 2004

Confirmation number: 5604

FOR: NOVEL METHOD FOR THE TREATMENT OF SYSTEMIC LUPUS ERYTHEMATOSIS

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BRIEF ON APPEAL

Hon. Commissioner of Patents
and Trademarks
PO Box 1450
Alexandria, VA 22313

Sir:

Responsive to the Final Office Action dated December 12, 2008, please consider this Brief on Appeal.

(i) Real Party of Interest

The real party of interest is the U.S. Government as represented by the Secretary of the Army.

(ii) Related Appeals and Interferences

There are no other related appeals and interferences.

(iii) Status of claims

Claims 1, 10, 11, 15, 29 and 30 are rejected and are the claims being appealed.

Claims 2-9, 12-14 and 16-28 are cancelled.

(iv) Status of amendments

There are no amendments filed after final rejection.

(v) Summary of claimed subject matter

The invention as presented in independent claim 1 is directed to a method of increasing IL-2 production in systemic lupus erythematosus T cells in a patient that has systemic lupus erythematosus comprising:

administering gene-modified T cells to the patient, the T cells originating from the patient and having been gene modified by treating them with antisense cAMP response element modulator (CREM) plasmid thereby increasing the expression of IL-2 in the T cells in the patient. (page 1, lines 12-23, page 5, lines 18-21, page 11, lines 5-17, page 13, lines 15-17, page 16, lines 6-15, page 38, lines 6-21)

The invention as presented in independent claim 10 is directed to a method of increasing IL-2 production in systemic lupus erythematosus lymphocytes in a patient having systemic lupus erythematosus comprising:

a) removing the lymphocytes from the patient;

b) leukophoresing the lymphocytes;

c) transfecting the leukorpheresed lymphocytes with plasmid vectors containing anti-sense cAMP response element modulator; and

d) re-infusing the transfected lymphocytes into the patient to increase IL-2 production in the lymphocytes in the patient. (page 1, lines 12-23, page 5, lines 18-21, page 11, lines 5-17, page 13, lines 15-17, page 16, lines 6-15, page 38, lines 6-21)

The invention as presented in independent claim 15 is directed to a method of increasing IL-2 production in systemic lupus erythemotosus T cells in a patient that has systemic lupus erythemotosus comprising: administering T cells from the patient that have been modified ex vivo to have decreased cAMP response element modulator mRNA to the patient. (page 1, lines 12-23, page 5, lines 18-21, page 11, lines 5-17, page 13, lines 15-17, page 16, lines 6-15, page 38, lines 6-21)

The invention as presented in independent claim 29 is a method of increasing IL-2 production in T cells from a systemic lupus erythematosus patient comprising:

removing the T cells from the patient; and

treating the T cells with antisense cAMP response element modulator (CREM); to increase IL-2 production in the T cells. (page 1, lines 12-23, page 16, lines 6-15)

The invention as presented in independent claim 30 is directed to a method of increasing IL-2 production in lymphocytes from a systemic lupus erythematosus patient comprising:

a) removing the lymphocytes from the patient;

b) leukophoresing the lymphocytes;

c) transfecting the leukophoresed lymphocytes with plasmid vectors containing anti-sense cAMP response element modulator to stop the expression of cAMP response element modulator and increase IL-2 production in the lymphocytes. (page 1, lines 12-23, page 5, lines 18-21, page 11, lines 5-17, page 13, lines 15-17, page 16, lines 6-15, page 38, lines 6-21.)

(vi) Grounds of rejection to be reviewed on appeal

Whether claims 1, 10-11, 15, 29 and 30 are patentable under 35 U.S.C. §103 (a) over Solomou et al., Weintraub, Monia et al, Symonds et al. and Gruenberg, et al.

(vii) Argument

The present invention is directed to a method of increasing IL-2 production in lymphocytes or T cells in a patient in vivo (claims 1, 10, 11, 15) or ex vivo (claims 29 and 30). Normal IL-2 production in T Cells is important. T Cells from patients with SLE have a greatly reduced production of IL-2. Applicants have successfully introduced anti-sense CREM into lymphocytes from a patient with SLE, decreased CREM production and increased IL-2 production in the T Cells (see Fig. 3, 5A and 6). Applicants have successfully treated T-cells with antisense CREM and enhanced the activity of the IL-2 promoter (Fig. 4, 4A, 4B, 4C, 5A). Applicants are the first to discover that antisense CREM would improve the production of IL-2 and that that decreased IL-2 production in SLE patients was not due to other positive transcriptional factors that bind to the IL-2 promoter.

None of the cited references, whether taken alone or in combination, would have provided the necessary teaching to enable and motivate one of ordinary skill in the art to arrive at the present invention because none of them conclude that CREM alone is responsible for decreased IL-2 production in SLE patients.

Solomou, et al. has been cited for its teaching of the discovery of the binding of CREM to the IL-2 promoter in SLE patients. The Examiner extrapolates that at the time of the invention, one of ordinary skill in the art would have concluded that reducing CREM production would increase IL-2 production in SLE patients. Appellants disagree.

Solomou et al. reported decreased IL-2 production in T cells of Lupus patients. Solomou et al. also reported that Lupus patients showed increased amounts of phosphorylated camp-responsive element modulator (p-CREM) bound to the -180 site of the IL-2 promoter, inhibiting the production of normal levels of IL-2. However, this was very early work. CREM and CREB are normal compounds found in humans. It was not known why CREM bound to the IL-2 promoter in Lupus patient's T-cells. It was not known at that time how to stop CREM from binding to the IL-2 promoter. In fact, at the time of the Solomou et al. paper, much was unknown about the pathways of CREM binding in Lupus patients. The following excerpt demonstrates the uncertainty of science at the time.

"The mechanism responsible for increased expression of CREM in SLE T cells remains unknown. It is fascinating that the same cells display decreased levels of certain molecules (e.g., TCR ζ-chain and p65 Rei A protein), but increased levels of other (e.g., CD40 ligand and cmyc proto-oncogene) (4). The pathways responsible for the phosphorylation of CREM in SLE T cells are also not known. The phosphorylation pattern of various cytosolic SLE T cell proteins is aberrant (19), and the activities of protein kinase A isozymes I and II (28, 29) and C (30) that phosphorylate CREB on Ser are decreased. The complete characterization of pathways involved in the phosphorylation of CREM may decipher its role in the transcriptional regulation of SLE

T cells genes. **Also, it is unclear at this point why the levels of p-CREM decrease in SLE T cells following stimulation.**" (Emphasis added.)

Solomou et al. also speculates that genes located in the identified SLE susceptibility loci could affect the expression and function of CREM and CREB (page 4222, col. 1). Finally, Solomou et al. concludes that, "Additional studies are needed to understand the mechanisms that lead to the increased levels of p-CREM in SLE and whether it interacts with other positive transcription factors that bind to the IL-2 promoter." (page 4222, col. 1) From these statements, it is evident that the solution is far from simple and that one of ordinary skill in the art at the time of the invention would have understood that multiple transcriptional factors could be the problem. There is no support provided in Solomou et al. that using antisense CREM would help SLE patients. To the contrary, it is clear from a reading of Solomou et al. that the solution could be found in addressing the mechanisms that lead to increased pCREM (to make the production normal) and a discovery of the other positive transcription factors that bind to the IL-2 promoter.

The Examiner looks to Weintraub for a solution to the questions prompted by Solomou et al. Weintraub is directed to basic teachings that molecules that bind with specific mRNA can selectively turn off genes. Weintraub refers to the use of silencing RNAs (sRNA) to silence the expression of specific RNAs and speculates that this may someday be useful technology. Weintraub is very general in its teachings. It only speculates that *viral diseases* or *dangerously mutated oncogenes* might be treated. (page 45 upper left column). Notably, it does not suggest that diseases wherein defective genes are present in lymphocytes or other naturally occurring cells of the human body could be

treated. It also does not provide any guidance on whether such treatment would even be harmful to patients in vivo. With the limited teachings in Weintraub, it would have been too large of a leap in science at the time of the invention to speculate that the "silencing RNA" of Weintraub that have only been associated with viral disease or oncogenes would operate the same way in T-cells that are part of the immune system. The type of cells are so different that one could not speculate that the antisense of Weintraub would be effective in reducing Solomou et al. CREM binding to the IL-2 promoter in lymphocytes.

Weintraub simply does not indicate how to solve the problem that Solomou defines. There is no way to determine or predict that the methods in Weintraub would have increased IL-2 production in humans and would result in benefiting SLE patients.

Further, the literature at the time and available to one of ordinary skill in the art actually taught against such reasoning as follows:

"Antisense compounds once seemed the answer to drug designers' dreams: molecules precisely tailored to block specific genes. But researchers have run into unexpected difficulties, and they are no longer sure what antisense drugs are doing inside the body." *Research News, Trisha Gura, Science 27 October 1995; vol. 270, no. 5236, pp. 575-577, DOI: 10.1126/science.270.5236.575.*

" 'While many successful antisense experiments have been reported in the literature, significant obstacles to widespread therapeutic use remain.' Wrote Dr. Cy Stein, Irving Assistant Professor of Medicine and Pharmacology, in 992 in the journal Leukemia. At the time Dr. Stein was criticized by some in industry for dampening an exciting technological breakthrough. Today, after several years of research in the area, investigators have come to realize that Dr. Stein is essentially correct; while the theory is valid, there are practical difficulties that must be overcome before antisense oligonucleotide technology realizes its promise." *Research Advance: common Sense About Antisense, Biomedical Frontiers: Fall 1995, vol. 3, no. 1, Expanded Genome Project*

"One advantage of using antisense therapy in treating infectious diseases such as virus infections is that it can be tailored to the particular strain in circulation, and then

modified as the virus mutates. One difficulty in applying this therapy is successfully delivering the antisense DNA or RNA to all target tissues (for instance, making sure the antisense strands reach infected blood cells for HIV). Another problem is maintaining prolonged suppression of target protein expression, since the antisense molecule will eventually be degraded by the cell's nuclease enzymes. One strategy to prevent degradation is to chemically modify the DNA to interfere with nuclease action." *Antisense Nucleotides, Genetics , 2003, Robinson, Richard*

Therefore, the combination of Weintraub's antisense technology with the Solomou, et al. early studies would not have motivated one of ordinary skill in the art to use antisense to correct IL-2 production. This is because of the many problems associated with antisense technology at the time and also because of the fact that all of the biological pathways leading to decreased IL-2 production were not completely understood as per Solomou et al.

Similarly, Monia et al. deals with antisense modulation of SMAD7 expression. SMAD 7 was isolated from cultured human vascular endothelial cells. SMAD7 regulates modulating endothelial gene expression. Endothelial cells are totally different than immunological T-cells described by Solomou or the present invention. T-cells function to solve complex immunology problems. There is no disclosure or suggestion of whether Monia et al.'s method would be useful in Solomou's T-cells or would have any affect on IL-2 production. There is also no suggestion that antisense technology is effective for all types of cells which is needed to make up for the deficiency of Weintraub. There is also no disclosure or suggestion of whether or not administering gene-modified T cells treated with antisense cAMP response element modulator plasmid would actually increase the production of IL-2 in patients with SLE in vivo or whether other factors existed that effected IL-2 production (see Solomou et al. quote above). Therefore, neither Monia nor

Weintraub established that antisense CREM would have increased IL-2 production in human T cells in SLE patients. This is especially true because Solomou et al. states: "Also, it is unclear at this point why the levels of CREM **decrease** in SLE T cells following stimulation." (page 4221, bottom of column 2) This statement alone would have led one of ordinary skill in the art away from trying the use of anti-sense CREM to treat SLE T cells.

Symonds et al. has also been cited by the Examiner for the proposition that antisense would have been the cure for any disease that had a symptom of a high level of a protein. Symonds et al. proposes transfection of CD34 proginitor cells (not terminally differentiated T cells in Solomou or the present invention). The proginator cells are very difficult to gene modify. Symonds et al., like Weintraub and Monia, is not directed to the claimed highly complex immunological T cells. Symonds et al. did not solve the mystery of why CREM is increased in SLE T cells or whether there were other transcriptional factors that effect IL-2 production or why CREM production decreased in SLE patients following stimulation.

Gruenberg is the only reference cited by the Examiner that relates to T-Cells. Gruenberg stimulated T cells in vitro with polyclonal stimulators (CD3, CD28). Unlike the present invention, Gruenberg operated without any growth factors like IL-2 or IFN-γ present. Also unlike the present invention, Gruenberg frequently re-stimulated T cells or T cell subset with immobilized anti-CD3 and anti-CD28 mAb to cause them to proliferate and differentiate into a highly pure population of activated memory Th1 cells. Gruenberg required re-stimulation every 2-3 days and that re-stimulation must be repeated at least 3 and typically 4 times in order to obtain a pure population of activated Th1 memory cells.

Activation with these antibodies greater than 5 times, however, results in diminishing cytokine production and increased activation-induced cell death. (page 2, paragraph 0017). Gruenberg's approach is that of polyclonal activation in vitro and although it may increase Th1 cytokines, the response varies from individual to individual and, therefore, is unpredictable. It is very different than the present invention. Gruenberg clarifies that the present invention is not simple science but an invention that really required extraordinary experimentation and testing to discover a remedy for SLE T Cell molecular problems. Therefore, Gruenberg does not make up for the deficiencies of Symonds, Monia, and Weintraub or lead one of ordinary skill in the art to conclude that antisense would be effective in T-Cells in vivo. More importantly, Gruenberg does not overcome Symonds, Monia and Weintraubs lack of teaching that CREM is the only reason that IL-2 production is decreased in SLE patients.

The presently claimed invention silences a protein in SLE T cells using in vitro gene transfer in order to specifically increase IL-2 production. It corrects the T-cells not just activates them. There is absolutely no overlap of the claimed invention and Gruenberg. Gruenberg does, however, demonstrate the difficulty experienced in the art of studying T cells. It also demonstrates the difficulty in working with the genetic mechanisms in T cells (increased activation-induced cell death).

Although a person of ordinary skill in the art would have appreciated from Solomou et al. that it is desirable to increase IL-2 production in SLE patients and that CREM causes decreased IL-2 production, neither Solomou et al nor the combined teachings of Weintraub, Monia e tal, Symonds et al. or Gruenberg provide any guidance to the skilled artisan on how to modify T cells with antisense CREM in such a way that

they will actually increase IL-2 production or whether other factors were contributing. Therefore, the invention is more than the predictable use of prior art elements. As shown from Gruenberg, such variables as the frequency of treatment can greatly affect cell death.

The Examiner's case of obviousness has been successfully rebutted because Gruenberg, Weintraub, Monia and Symonds et al, do not suggest that antisense would be effective in treating T-Cells, or that that using it would result in normal IL-2 production.

Despite the early promise of gene therapy, there has been little success despite massive efforts in the last decade. This is due at least in part to low efficiencies of gene transfer, an inability to modify enough cells, an inability to target appropriate cell types, and a lack of persistence of the desired effect in human subjects. (Symonds, Column 1, lines 54-60). In light of this problem, Symonds leads the artisan to believe that the solution to SLE is not easy. Symonds does not indicate how to modify the teachings of Weintraub or Mania to provide a procedure that could be expected to produce successful results including high efficiencies of gene transfer in T cells.

The Examiner's combination of references is based on hindsight.

viii. Claims Appendix

1. A method of increasing IL-2 production in systemic lupus erythematosus T cells in a patient that has systemic lupus erythematosus comprising:

administering gene-modified T cells to said patient, said T cells originating from said patient and having been gene modified by treating them with antisense cAMP response element modulator (CREM) plasmid thereby increasing the expression of IL-2 in said T cells in said patient.

2.- 9. (cancelled)

10. A method of increasing IL-2 production in systemic lupus erythematosus lymphocytes in a patient having systemic lupus erythematosus comprising:

a) removing said lymphocytes from said patient;

b) leukophoresing said lymphocytes;

c) transfecting said leukorpheresed leukophoresed lymphocytes with plasmid vectors containing anti-sense cAMP response element modulator; and

d) re-infusing said transfected lymphocytes into the patient to increase IL-2 production in said lymphocytes in said patient.

11. The method of claim 10, wherein said antisense cAMP response element modulator, is α-antisense cAMP response element modulator that prevents CREM mRNA from being transcribed and forming CREM protein.

12.-14 (cancelled)

15. The method of increasing IL-2 production in systemic lupus erythemotosus T cells in a patient that has systemic lupus erythemotosus comprising: administering T cells

from said patient that have been modified ex vivo to have decreased cAMP response element modulator mRNA to said patient.

16-28 (cancelled)

29. A method of increasing IL-2 production in T cells from a systemic lupus erythematosus patient comprising:

removing said T cells from said patient; and

treating said T cells with antisense cAMP response element modulator (CREM); to increase IL-2 production in said T cells.

30. A method of increasing IL-2 production in lymphocytes from a systemic lupus erythematosus patient comprising:

a) removing said lymphocytes from said patient;

b) leukophoresing said lymphocytes;

c) transfecting said leukophoresed lymphocytes with plasmid vectors containing anti-sense cAMP response element modulator to stop the expression of cAMP response element modulator and increase IL-2 production in said lymphocytes.

ix. Evidence Appendix

1. Declaration under 37 CFR 1.132 signed by Dr. George Tsokos dated October 15, 2007.

Serial No. 10/772,704

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of

TSOKOS, GEORGE C. *et al.*

Group Art Unit: 1635

Examiner: Chong, Kimberly

Appl. No. 10/772,704

Filing Date: February 5, 2004

Confirmation No.: 5604

Title: NOVEL METHOD FOR THE TREATMENT OF SYSTEMIC LUPUS ERYTHEMATOSIS

DECLARATION UNDER 37 CFR 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In response to the Office Action dated September 27, 2007, Applicants submit this Declaration under section 1.132 to show that the inventorship of the application is correct and that the reference cited against the present claims, namely, Tenbrock, et al. "Antisense Cyclic Adenosine 5'-Monophosphate Response Element Modulator Up-Regulates IL-2 in T Cells from Patients with Systemic Lupus Erythematosus, Journal of Immunology, 2002, ("Tenbrock et al. reference") presents subject matter derived from the applicants rather than invented by another.

1. We, Dr. George C. Tsokos and Dr. Yuang-Taung Juang, declare as follows:

2. We are the only and correctly named inventors in the above referenced application.

3. We are authors of the "Tenbrock et al. reference" and first conceived all of the subject matter described therein.

4. The other named authors of the "Tenbrock et al. reference", Klaus Tenbrock, Mark F. Gourely, and Madhusoodana P. Nambiar, provided laboratory assistance and performed experiments under our direction but did not contribute to the conception of the claimed invention.

5. We further declare that all statements made herein of our own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the above-referenced application or any patent issuing thereon.

George C. Tsokos — Date: Oct 15, 2007

Yuang-Taung Jueng — Date: Oct 15, 2007

x. Related Proceedings Appendix

There are no related proceedings.

Reconsideration and the granting of this appeal is respectfully requested.

Respectfully submitted,

Date: June 19, 2009 By

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